Author's response to reviews

Title: Pilot study evaluating broccoli sprouts in advanced pancreatic cancer [POUDER trial] - study protocol for a randomized controlled trial

Authors:

Vladimir J Lozanovski (vladimir.lozanovski@med.uni-heidelberg.de)
Philipp Houben (philipp.houben@med.uni-heidelberg.de)
Ulf Hinz (ulf.hinz@med.uni-heidelberg.de)
Thilo Hackert (thilo.hackert@med.uni-heidelberg.de)
Ingrid Herr (i.herr@dkfz.de)
Peter Schemmer (peter.schemmer@med.uni-heidelberg.de)

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Author's response to reviews: see over
Reviewer's report:

This is a very well written protocol for a clearly defined study which has the potential to show some interesting results. The manuscript is concise yet detailed, and the protocol is nicely put together. I have some comments on the manuscript which, if addressed, may improve the quality of the protocol further. These should all be considered major compulsory revisions unless otherwise stated.

Major compulsory revisions

1. Abstract, discussion: the authors state that ‘although no significant results may be observed in this pilot trial...’ A pilot trial should not be looking to demonstrate significance on any of the trial parameters, so this sentence should be modified accordingly.

- Answer: indeed, the goal of a pilot trial is to mainly test the feasibility of the tested methods and to serve as a base for a confirmatory trial. The sentence has been deleted.

- Changes in the manuscript: the POUDER trial is expected to transfer promising experimental and epidemiological data into a clinical pilot study to assess the effectiveness of broccoli sprout extracts in the treatment of advanced PDA. The study objectives will provide data on the clinical feasibility and acceptability of a supportive treatment option accompanying palliative chemotherapy. Based on these results, future clinical studies to create further evidence in this field are possible.

2. Methods, para 1: the text says that ‘Due to the nutrition supplemental character of the trial, sufficient oral intake is a prerequisite for inclusion in the study’. I was not clear on what the authors mean here, so some clarification or rewording would be useful.

- Answer: we thank the reviewer for the remark. Based on the necessity of daily oral intake of 15 capsules, the patients should not have problems with oral food and beverage intake i.e. no nausea and/or vomitus should be present. In this context, the presence of nasogastric tube is an exclusion criterion.

- Changes in the manuscript: due to the nutrition supplemental character of the trial, sufficient oral intake is a prerequisite for inclusion in the study i.e. the patients should not have symptoms or signs of indigestion or problems with the passage of food (nausea, vomitus, presence of nasogastric tube) (Table 1).
3. Methods, trial objectives, para 1: the primary objective of the trial is given at the start of the paragraph. However, technically, the remainder of the paragraph describes the outcome measures for which data will be collected. After stating the objective, I would suggest having a new heading of ‘outcome measures’, followed by a bullet pointed list of the outcome measures to be assessed.

- Answer: indeed, a new “Outcome measures” heading provides with a better overview and differentiation between objectives and measures. However, a bullet has been omitted since the outcome measures and the time-schedule have already been depicted in Figure 1.

- Changes in the manuscript: new “Outcome measures” heading has been added.

4. Following the previous point, the abstract states that feasibility of the study substance will be assessed (I took this to mean in terms of the acceptability to patients of taking 15 capsules a day of the study substance/placebo). However, there is currently no mention of this in the methods section as one of the outcomes that will be assessed.

- Answer: the remark is much appreciated. Under paragraph Trial objectives an additional sentence clarifying the test of the abovementioned feasibility has been added.

- Changes in the manuscript: the objective of this pilot trial is to evaluate the feasibility of nutritional supplements rich in sulforaphane and quercetin, administered via encapsulated, freeze-dried broccoli sprouts, in patients with advanced pancreatic cancer undergoing treatment with palliative chemotherapy. In this context, given the number of 15 capsules per day that patients are supposed to take, the principal objective of this trial is to test if the daily intake is possible. In order to achieve the effective Sulforaphane dose as extrapolated from our previous animal experiments, the capsules should be taken all 15 at once, however with an acceptable pause of few minutes in between.

5. Trial interventions paragraph: the text states that patients will be expected to have 15 capsules a day of the active substance or placebo treatment. However, no more detail beyond this is given about the expected intake protocol. For example, will patients be expected to take one capsule at a time at regular intervals throughout the day (e.g. once per hour over 15 hours), or will patients be able to take multiple capsules at a time at longer intervals (e.g. 5 capsules 3 times a day). As this detail could have a significant impact on patient perceptions of the acceptability of the trial substance in terms of the effect it has on their daily lives, this is an important detail to clarify.

- Answer: this has already been commented and modified. We kindly please you to
refer to the answer to Remark 4.

- **Changes in the manuscript**: in this context, given the number of 15 capsules per day that patients are supposed to take, the principal objective of this trial is to test if the daily intake is possible. In order to achieve the effective Sulforaphane dose as extrapolated from our previous animal experiments, the capsules should be taken all 15 at once, however with an acceptable pause of few minutes in between.

6. **Randomisation and blinding para**: the text states that in the case of dropouts, patients will be replaced and new patients assigned. First, can the authors clarify whether partial data for patients who have withdrawn will be used (e.g. if a patient drops out at month 6, will their first 6 months’ of data be included in analysis, or will that patient be removed from the trial completely, including any data that they have generated prior to their withdrawal). Second, replacing a dropout patient with a new patient has implications for the length of the trial e.g. if a patient drops out at month 9, replacing them with a new patient at such a late stage may not be possible. Will the research team place a limit on the point in the trial at which it is feasible to replace patients who have withdrawn with new patients (e.g. only those who drop out in the first 3 months), or will such replacements be undertaken right up towards the end of the follow up period?

- **Answer**: we thank the reviewer for this important remark and added the following information to the manuscript

- **Changes in the manuscript**: If a patient drops out of the study at month 6 due to his/her own decision, the patient data will be removed from the trial completely, including any data generated prior to the withdrawal. If patient passes away during the first 6 months, the data will be used. If the urine probes reveal that a patient from the broccoli sprouts group did not consume the broccoli sprouts daily or if a patient from the placebo group had a high dietary intake of isothiocyanates, the data from these patients will not be used, but the patient will be replaced by a new patient, even if a patient drops out between month 9-12. This case will extend the duration of the study.

7. **Sample size**: although the authors are correct that a sample size calculation is not necessary for the pilot trial, it would still be good practice to give a reason for the choice of 20 patients per study arm over and above the fact that 20 per group is ‘deemed sufficient for the study objectives’. At least a reference supporting this as a reasonable number of participants for a trial of this nature is needed.

- **Answer**: we agree that the sample size of 20 patients per group is speculative at this time and the number of enrolled patients is based on comparable numbers in similar ongoing patient studies with broccoli sprout extracts. E.g. the Pittsburgh pilot study evaluating sulforaphane in atypical nevi-precursor lesions enrolled 18 patients (http://clinicaltrials.gov/ct2/show/NCT01568996?term=NCT01568996&rank=1) and another study performed at OHSU Knight Cancer Institute for examination of

- **Changes in the manuscript:** The sample size of 20 patients per group is speculative at this time and it is based on comparable patient numbers used in similar ongoing and just completed patient studies with broccoli sprout extracts. E.g. the Pittsburgh pilot study evaluating sulforaphane in atypical nevi-precursor lesions enrolled 18 patients (clinicaltrials.gov/ct2/show/NCT01568996?term=NCT01568996&rank=1) and another study performed at OHSU Knight Cancer Institute for examination of sulforaphane in treating patients with recurrent prostate cancer (clinicaltrials.gov/ct2/show/record/NCT01228084?term=sulforaphane&rank=1) enrolled 20 patients.

8. **Discussion, para 5:** the sentence that begins ‘Since patients suffering’ seems to have some words missing as ‘...other phytotherapies are may be expected’ does not make sense.

- **Answer:** we are thankful for this notation on the grammatical error. The sentence has been modified adequately.

- **Changes in the manuscript:** since patients suffering from tumor diseases are often encouraged to make healthy changes in their lifestyle, other phytotherapies may be expected.

9. **Tables and figures:** I’m not sure that Table 2 adds anything to the protocol. This is a simple two-arm, parallel trial with a small number of patients in each group. The number in each group, and the distinction between placebo and active substance as an intervention is already perfectly clear from the existing text without Table 2 being necessary, so I would suggest removing it from the manuscript.

- **Answer:** we agree with the redundancy of the Table 2.

- **Changes in the manuscript:** Table 2 has been removed from the manuscript.